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Cerclage for sonographic short cervix in singleton gestations without prior spontaneous preterm birth: systematic review and meta-analysis of randomized controlled trials using individual patient-level data

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KEYWORDS: cervical length; intensive care; prematurity; preterm birth; transvaginal ultrasound; ultrasound-indicated cerclage

ABSTRACT

Objective *The aim of this systematic review and meta-analysis was to quantify the efficacy of cervical cerclage in preventing preterm birth (PTB) in asymptomatic singleton pregnancies with a short mid-trimester cervical length (CL) on transvaginal sonography (TVS) and without prior spontaneous PTB.*

Methods *Electronic databases were searched from inception of each database until February 2017. No language restrictions were applied. All randomized controlled trials (RCTs) of asymptomatic singleton pregnancies without prior spontaneous PTB, found to have short CL < 25 mm on mid-trimester TVS and then randomized to management with either cerclage or no cerclage, were included. Corresponding authors of all the included trials were contacted to obtain access to the data and perform a meta-analysis of individual patient-level data. Data provided by the investigators were merged into a master database constructed specifically for the review. Primary outcome was PTB < 35 weeks. Summary measures were reported as relative risk (RR) with 95% CI. The quality of the evidence was assessed using the GRADE approach.*

Results *Five RCTs, including 419 asymptomatic singleton gestations with TVS-CL < 25 mm and without prior spontaneous PTB, were analyzed. In women who were randomized to the cerclage group compared with those in the control group, no statistically significant differences were found in PTB < 35 (21.9%* vs *27.7%; RR, 0.88 (95% CI 0.63–1.23);* $I^2 = 0\%$*; five studies, 419 participants), < 34, < 32, < 28 and < 24 weeks, gestational age at delivery, preterm prelabor rupture of membranes (PPROM) and neonatal outcomes. In women who received cerclage compared with those who did not, planned subgroup analyses revealed a significantly lower rate of PTB < 35 weeks in women with TVS-CL < 10 mm (39.5%* vs *58.0%; RR, 0.68 (95% CI, 0.47–0.98);* $I^2 = 0\%$*; five studies; 126 participants) and in women who received tocolytics (17.5%* vs *32.7%; RR, 0.54 (95% CI, 0.31–0.93);* $I^2 = 0\%$*; four studies; 169 participants) or antibiotics (18.3%* vs *31.5%; RR, 0.58 (95% CI, 0.33–0.98);* $I^2 = 0\%$*; three studies; 163 participants) as additional therapy to cerclage. The quality of evidence was downgraded two levels because of serious imprecision and indirectness, and therefore was judged as low.*

Conclusions *In singleton gestations without prior spontaneous PTB but with TVS-CL < 25 mm in the second trimester, cerclage does not seem to prevent preterm delivery or improve neonatal outcome. However, in these pregnancies, cerclage seems to be efficacious at lower CLs, such as < 10 mm, and when tocolytics or antibiotics are used as additional therapy, requiring further*

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studies in these subgroups. Given the low quality of evidence, further well-designed RCTs are needed to confirm the findings of this study.

INTRODUCTION

Preterm birth (PTB) is a major cause of perinatal morbidity and mortality[1]. Worldwide, about 15 million babies are born too early every year, resulting in 1.1 million deaths as well as short- and long-term disabilities in countless numbers of survivors[2,3].

Few prognostic tests are available to predict PTB[4,5]. Short cervical length (CL) measured by transvaginal sonography (TVS) has been shown to be a good predictor of spontaneous PTB in both singleton and twin gestations[4–8].

Different strategies have been adopted for preventing PTB, including use of progesterone, cerclage and cervical pessary, as well as lifestyle modification, such as smoking cessation, diet, aerobic exercise and nutritional supplements[9–24]. The evidence supports the use of vaginal progesterone in singleton pregnancies with short cervix[9], while cervical cerclage seems to be beneficial only in the subgroup of singleton gestations with both prior spontaneous PTB and CL $\leq$ 25 mm[10], but not in singletons without prior PTB[11] or in multiple gestations[24]. Cervical pessary is relatively non-invasive and easy to use, as it does not require anesthesia, it can be inserted in an outpatient clinic setting and it can be easily removed if necessary. However, published data on the use of cervical pessary are contradictory, and meta-analyses have shown that it has no efficacy in the prevention of PTB in both singleton[13] and multiple[23] pregnancies.

Interestingly, only 235 women with singleton pregnancy without prior spontaneous PTB[11] and 504 women with singleton pregnancy and prior spontaneous PTB[10] have been included in meta-analyses of randomized controlled trials (RCTs) on cerclage for TVS-CL $<$ 25 mm. In an individual patient-level data (IPD) meta-analysis of four RCTs, Berghella *et al.* found a non-significant 16% reduction in PTB $<$ 35 weeks in singletons without prior spontaneous PTB but with a TVS-CL of $<$ 25 mm who were randomized to cerclage compared with no cerclage[11].

Recently, Otsuki *et al.* reported data from a new RCT on cerclage in women with short TVS-CL, including also singleton gestations without prior spontaneous PTB[25]. They showed that for women with TVS-CL $<$ 25 mm between 16 and 26 weeks of gestation, cerclage might be considered to reduce the occurrence of threatened PTB.

Our objective was to update and expand the previous IPD meta-analysis[11] and to evaluate the efficacy of cervical cerclage in preventing PTB and perinatal morbidity and mortality in asymptomatic singleton pregnancies with short CL on mid-trimester TVS and without prior spontaneous PTB.

METHODS

Search strategy

The review protocol was established by two investigators (V.B. and G.S.) before commencement of the study and was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42016048269).

The electronic databases MEDLINE, ClinicalTrials.gov, PROSPERO and the Cochrane Central Register of Controlled Trials were searched, from inception of each database until February 2017, using the terms 'cerclage', 'cervical cerclage', 'salvage cerclage', 'rescue cerclage', 'emergency cerclage', 'ultrasound-indicated cerclage', 'short cervix', 'cervical length', 'ultrasound' and 'randomized trial'. All manuscripts were reviewed for pertinent references. No language restrictions were applied.

Study selection

Selection criteria included RCTs of asymptomatic singleton pregnancies without prior spontaneous PTB found to have a mid-trimester CL $<$ 25 mm on TVS and then randomized to management with either cerclage (intervention group) or no cerclage (control group). Quasi-randomized trials (i.e. trials in which allocation was carried out on the basis of a pseudo-random sequence, such as odd/even hospital number or alternation of date of birth), studies on multiple pregnancies[24] and studies on symptomatic women were excluded. Trials evaluating history-indicated (prior spontaneous PTB) or physical examination-indicated (second-trimester cervical dilatation detected on physical examination) cerclage[26], trials on ultrasound-indicated (short TVS CL)[10,11,27] cerclage with prior spontaneous PTB, as well as studies on technical aspects of cervical cerclage[28], were also excluded.

Data extraction and risk-of-bias assessment

The risk of bias in each included study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[29]. Seven domains related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with biased estimates of treatment effect: (domain 1) random sequence generation; (domain 2) allocation concealment; (domain 3) blinding of participants and personnel; (domain 4) blinding of outcome assessment; (domain 5) incomplete outcome data; (domain 6) selective reporting; and (domain 7) other bias. Review authors' judgments were categorized as 'low risk', 'high risk' or 'unclear risk' of bias[29].

We contacted the corresponding authors of all included RCTs to request access to the data and perform a meta-analysis of IPD. The authors were asked to supply anonymized data (without identifiers) about patient baseline characteristics, experimental intervention,

control intervention, co-interventions and prespecified outcome measures for every randomly assigned subject and were invited to become part of the collaborative group with joint authorship of the final publication. Data provided by the investigators were merged into a master database constructed specifically for the review. Data were checked for missing information, errors and inconsistencies by cross-referencing the publications of the original trials. Quality and integrity of the randomization processes were assessed by reviewing the chronological randomization sequence and pattern of assignment, as well as the balance of baseline characteristics across treatment groups. Inconsistencies or missing data were discussed with the authors and corrections were made when deemed necessary.

Quality of evidence

For this review, the quality of the evidence was assessed using the GRADE approach in order to assess the quality of the body of evidence relating to the primary and secondary outcomes. The GRADEpro Guideline Development Tool was used to import data from Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias[29].

Outcomes

Primary and secondary outcomes were established *a priori*. The primary outcome was PTB < 35 weeks. Secondary outcomes were: PTB < 37, < 34, < 32, < 28 and < 24 weeks; gestational age at delivery; latency (time from randomization to delivery); incidence of PPROM; and neonatal outcomes, including birth weight (low if < 2500 g or very low if < 1500 g), respiratory distress syndrome, intraventricular hemorrhage (Grade 3 or Grade 4), sepsis, necrotizing enterocolitis, admission to neonatal intensive care unit (NICU), length of stay in NICU and neonatal death (i.e. death of a liveborn baby within the first 28 days). The primary outcome (PTB < 35 weeks) was assessed according to different TVS-CL cut-offs (≤ 20, ≤ 15, < 10 and < 5 mm) and according to race, type of cerclage and additional therapy used.

Data analysis

The data analysis was completed independently by two authors (V.B. and G.S.) using Review Manager 5.3. The completed analyses were then compared and any difference was resolved with review of the entire data and independent analyses. IPD were analyzed using the so-called two-stage approach. In this, the IPD are first analyzed separately in each study to produce study-specific estimates of relative treatment effect. A combined estimate is then obtained in the second step by calculating a weighted average (inverse error variance based) of the individual estimates using methods analogous to meta-analyses of aggregate data. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is caused by heterogeneity rather than chance. Meta-analysis was performed using the random-effects model of DerSimonian and Laird, to produce summary treatment effects in terms of either relative risk (RR) or mean difference (MD) with 95% CI. Potential publication biases were assessed statistically using Begg's and Egger's tests[30]. $P < 0.05$ was considered statistically significant.

Characteristics of the included women obtained in the merged database were analyzed using SPSS Statistics version 19.0 (IBM Inc., Armonk, NY, USA). Data are shown as mean ± SD or as n (%). Univariate comparisons of dichotomous data were performed using the chi-square or Fisher's exact tests. Comparisons between groups were performed using the t-test to test group means with SD. A two-sided value of $P < 0.05$ was considered statistically significant.

All review stages were conducted independently by two reviewers (V.B. and G.S.). The two authors independently assessed the electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with a third reviewer (A.C.).

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement[31].

RESULTS

Study selection and population characteristics

A flowchart summarizing study identification and selection is shown in Figure 1. Five RCTs[25,32–35], including 419 asymptomatic singleton gestations with short mid-trimester TVS-CL and without prior spontaneous PTB, were included in the meta-analysis.

The overall risk of bias of the included trials was low (Figure 2). All studies had a low risk of bias in random sequence generation, incomplete outcome data and selective reporting. Adequate methods for allocation of women were used. All randomized women were included in an intention-to-treat analysis. Given the type of intervention, double-blinding was not feasible and all trials were judged as high risk in performance bias.

Publication bias, assessed using Begg's and Egger's tests, showed no significant bias ($P = 0.39$ and $P = 0.51$, respectively). Statistical heterogeneity between the studies was low ($I^2 = 0\%$) with no inconsistency in the primary and most of the secondary outcomes.

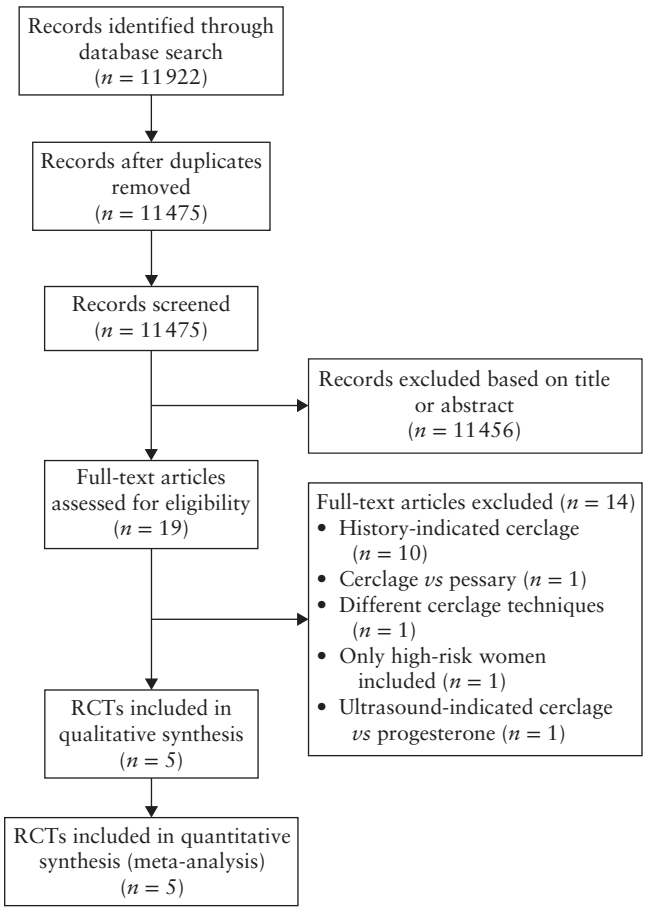

Figure 1 Flowchart summarizing inclusion of randomized controlled trials (RCTs) in this systematic review.

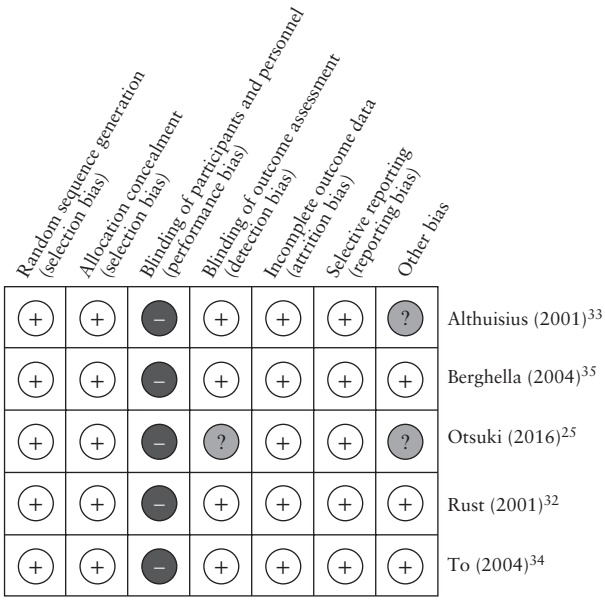

Figure 2 Risk of bias according to the Cochrane Handbook[29] in randomized controlled trials included in meta-analysis. Only first author is given for each study. Risk of bias: ⊕, low; ?, unclear; ⊖, high.

The characteristics of the included trials are shown in Table 1. All the included trials enrolled also women with prior spontaneous PTB who were excluded from the IPD meta-analysis. Multiple gestations were also excluded. Therefore, the IPD was used in order to include only singleton gestations without prior spontaneous PTB.

Of the 419 women analyzed, 224 (53.5%) were included in the cerclage group (intervention group) and 195 (46.5%) in the control (no-cerclage) group. Only singleton gestations without prior spontaneous PTB and with short cervix < 25 mm on TVS were analyzed. Most of the included studies (four of five)[25,32,33,35] defined short cervix as CL < 25 mm on TVS, while To *et al.*[34] defined this as TVS-CL ≤ 15 mm. Three trials[32,33,35] used only McDonald cerclage, To *et al.*[34] used only Shirodkar cerclage, while Otsuki *et al.*[25] used either McDonald or Shirodkar cerclage (Table 1). All studies used the transvaginal approach for cerclage. None of the 419 women received progesterone.

In the study by Berghella *et al.*[35], administration of indomethacin (100 mg loading dose rectally, perioperatively, followed by 50 mg every 6 h for 48 h orally, postoperatively) was left to the discretion of the obstetrician, while antibiotics were not used. In the study by Althuisius *et al.*[33], all women in the cerclage group received perioperative antibiotics (amoxicillin/clavulanic acid 1 g intravenously four times daily and metronidazole 500 mg intravenously three times daily for 24 h, followed by amoxicillin/clavulanic acid 500 mg four times daily and metronidazole 500 mg three times daily for 6 days, orally) and indomethacin suppository (100 mg, 2 h before and 6 h after the operation). In the study by Rust *et al.*[32], before randomization, all women were placed on inpatient bed rest for 48–72 h and were treated identically with amniocentesis, multiple urogenital cultures and 48–72 h of therapy with indomethacin (100 mg loading dose rectally, followed by 50 mg orally every 6 h) and clindamycin (900 mg intravenously every 8 h). No interventions, including tocolytics, antibiotics and bed rest, were recommended routinely in the study by To *et al.*[34]. In the study by Otsuki *et al.*[25], all women randomized in the cerclage group received tocolytic agents (usually ritodrine 100 μg/min intravenously until the day after the operation and for no longer than 2 days) and ampicillin (2 g/day for 2 days). In the same trial, bed rest was recommended for both groups for at least 7 days, and all patients were discharged from the hospital after 2 weeks from admission or operation[25]. Rust *et al.*[32], Althuisius *et al.*[33], Otsuki *et al.*[25] and Berghella *et al.*[35] routinely recommended similar activity restriction for women in both the intervention and the control groups.

Women who received cervical suture had it removed at 36 + 0 to 37 + 6 weeks of gestation, unless spontaneous onset of labor, rupture of the membranes or need for early delivery occurred.

In both groups, mean gestational age at randomization was about 22 weeks (22.5 ± 2.0 weeks *vs* 22.2 ± 2.2 weeks) and mean TVS-CL was about 12 mm (12.6 ± 6.4 mm *vs* 12.7 ± 6.3 mm) (Table 2).

Table 1 Characteristics of randomized controlled trials included in this systematic review and meta-analysis comparing effectiveness of use of cervical cerclage *vs* no cerclage in preventing spontaneous preterm birth (PTB) in singleton pregnancies with short mid-trimester cervical length (CL) on transvaginal sonography (TVS) and without prior spontaneous PTB

Reference	*Country*	*Sample size* (n)*	*GA at randomization (weeks)*	*Definition of short TVS-CL*	*Type of cerclage*	*Cerclage suture*	*Definition of prior spontaneous PTB (weeks)*	*Primary outcome*	*Lost to follow-up (%)*
Rust (2001)[32]	USA	105 (51 *vs* 54)	16–24	< 25 mm	McDonald	Permanent monofilament	16–36	PTB < 34 weeks	0
Althuisius (2001)[33]	Netherlands	9 (5 *vs* 4)	14–27	< 25 mm	McDonald	Braided tape	17–33	PTB < 34 weeks	0
To (2004)[34]	Multicenter†	209 (106 *vs* 103)	22–24	≤ 15 mm	Shirodkar	Braided tape	16–32	PTB < 33 weeks	0.4
Berghella (2004)[35]	USA	21 (9 *vs* 12)	14–24	< 25 mm	McDonald	Braided tape	16–34	PTB < 35 weeks	0
Otsuki (2016)[25]	Japan	75 (53 *vs* 22)	16–26	< 25 mm	McDonald ($n = 27$), Shirodkar ($n = 26$)	Braided tape	16–36	GA at delivery	0

Only first author is given for each study. *Cerclage group *vs* no-cerclage group. †UK, Brazil, South Africa, Slovenia, Greece and Chile. GA, gestational age.

Table 2 Characteristics of 419 women with singleton pregnancy, with short mid-trimester cervical length (CL) on transvaginal sonography (TVS) and without prior spontaneous preterm birth (PTB) included in randomized controlled trials and randomized to management with cerclage or no cerclage to prevent spontaneous PTB

Characteristic[ref]	*Cerclage* (n = *224*)	*No cerclage* (n = *195*)	P
Age (years)[25,32–35]	29.6 ± 6.3	29.7 ± 6.5	0.72
Prior cone[33,35]	3/14 (21.4)	4/16 (25.0)	0.58
Race[32–35]			0.75
White	95/171 (55.6)	88/173 (50.9)	
Black	57/171 (33.3)	68/173 (39.3)	
Other*	19/171 (11.1)	17/173 (9.8)	
Mullerian anomalies[33,35]	1/14 (7.1)	0/16 (0.0)	0.44
Smoking[25,33–35]	18/173 (10.4)	16/141 (11.3)	0.70
GA at randomization (weeks)[25,32–35]	22.5 ± 2.0	22.2 ± 2.2	0.27
CL on TVS (mm)[25,32–35]	12.6 ± 6.4	12.7 ± 6.3	0.93
Mode of delivery[25,33–35]			0.08
Vaginal	135/173 (78.0)	122/141 (86.5)	
Cesarean section	38/173 (22.0)	19/141 (13.5)	

Values are given as mean ± SD or *n*/*N* (%). *Asian, Hispanic. Some data are missing as not all variables were recorded in every database. GA, gestational age.

Synthesis of results

No statistically significant differences were found for the primary outcome (PTB < 35 weeks) (Table 3, Figure 3) or the secondary outcomes (Table 3, Figure 4) comparing women who were randomized to the cerclage group with those who were randomized to the control group.

In women who received cerclage compared with those who did not, planned subgroup analyses revealed a significant decrease in PTB < 35 weeks in women with TVS-CL < 10 mm (39.5% *vs* 58.0%; RR, 0.68 (95% CI, 0.47–0.98)) (Table 4; Figure 5), women who were white (22.1% *vs* 37.5%; RR, 0.59 (0.37–0.94)) and in those who received tocolytics (17.5% *vs* 25.7%; RR, 0.61 (95% CI, 0.38–0.98)) or antibiotics (18.3% *vs* 31.5%; RR, 0.58 (95% CI, 0.33–0.98)) as additional therapy to cerclage (Table 4; Figure 6).

The quality of evidence was downgraded because of serious imprecision (Table 3). Outcomes were imprecise because studies included relatively few patients and few events, and thus had wide confidence intervals around the estimate of the effect, and because the optimal information size was not reached. The quality of the evidence was also downgraded another level because of serious indirectness owing to different study designs.

DISCUSSION

Main findings

This IPD meta-analysis of five RCTs, including 419 women, showed that transvaginal cervical cerclage did not reduce the rate of PTB or improve neonatal outcome in asymptomatic singleton pregnancies with mid-trimester TVS-CL < 25 mm and without prior spontaneous PTB. Planned subgroup analyses revealed a significant decrease in PTB < 35 weeks in women with TVS-CL < 10 mm and when tocolytics or antibiotics were used as additional therapy.

The quality level of summary estimates was judged low, as assessed by GRADE, indicating that the true effect may, or is even likely to, be substantially different from the estimate of the effect.

Our data support earlier findings of a prior meta-analysis by Berghella *et al.*[11]. This review showed that cerclage did not prevent preterm delivery in the overall population of singletons with short TVS-CL but without prior spontaneous PTB.

Strengths and limitations

One of the strengths of this meta-analysis is that we included all RCTs published so far on the topic, including

Table 3 Primary and secondary outcomes of randomized controlled trials included in this systematic review and meta-analysis comparing effectiveness of use of cervical cerclage *vs* no cerclage in preventing spontaneous preterm birth (PTB) in 419 singleton pregnancies with short mid-trimester cervical length (CL) on transvaginal sonography (TVS) and without prior spontaneous PTB

Outcome[ref]	*Cerclage (n = 224)*	*No cerclage (n = 195)*	*RR or MD (95% CI)*	I^2 *(%)*	*Q-statistic*	*Quality of evidence*
PTB < 35 weeks[25,32–35]	49/224 (21.9)	54/195 (27.7)	0.88 (0.63 to 1.23)	0	2.09	Low
PTB < 37 weeks[25,32–35]	81/224 (36.2)	80/195 (41.0)	0.93 (0.73 to 1.18)	57	4.84	Low
PTB < 34 weeks[25,32–35]	45/224 (20.1)	49/195 (25.1)	0.89 (0.63 to 1.27)	0	0.67	Low
PTB < 32 weeks[25,32–35]	38/224 (17.0)	39/195 (20.0)	0.96 (0.64 to 1.42)	0	0.62	Low
PTB < 28 weeks[25,32–35]	26/224 (11.6)	22/195 (11.3)	1.15 (0.68 to 1.93)	0	0.52	Low
PTB < 24 weeks[25,32–35]	5/224 (2.2)	4/195 (2.0)	1.14 (0.36 to 3.63)	0	0.69	Low
GA at delivery (weeks)[25,32–35]	35.81	35.59	0.22 (−0.58 to 1.02)	0	2.02	Low
Latency (days)[25,32–35]	86.68	83.41	3.27 (−3.22 to 9.76)	50	8.14	Low
PPROM[32,34,35]	34/166 (20.5)	23/169 (13.6)	1.52 (0.94 to 2.46)	0	1.21	Low
Birth weight (g)[25,32–35]	2635	2540	94.65 (−146.23 to 335.53)	0	0.41	Low
LBW[25,32–35]	42/224 (18.8)	49/195 (25.1)	0.88 (0.44 to 1.74)	52	9.41	Low
VLBW[25,32–35]	22/224 (9.8)	21/195 (10.8)	0.97 (0.57 to 1.68)	0	0.84	Low
RDS[33,35]	2/14 (14.3)	2/16 (12.5)	1.33 (0.23 to 7.74)	0	1.34	Low
IVH[33,35]	1/14 (7.1)	0/16 (0.0)	3.90 (0.18 to 85.93)	0	1.27	Low
Sepsis[33,35]	2/14 (14.3)	2/16 (12.5)	1.33 (0.23 to 7.74)	0	0.67	Low
NEC[33,35]	0/14 (0.0)	0/16 (0.0)	NA	NA	NA	Low
NICU[25,33,35]	3/67 (4.5)	4/38 (10.5)	0.80 (0.26 to 2.47)	31	6.41	Low
LOS in NICU (days)[33,35]	25.2	14.9	10.30 (−27.35 to 47.95)	0	2.34	Low
Neonatal death[25,32,33,35]	7/118 (5.9)	6/92 (6.5)	1.08 (0.41 to 2.86)	0	1.21	Low

Values are given as mean or *n/N* (%), unless stated otherwise. Some data are missing as not all variables were recorded in every database. GA, gestational age; IVH, intraventricular hemorrhage; LBW, low birth weight; LOS, length of stay; MD, mean difference; NA, not applicable; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PPROM, preterm prelabor rupture of membranes; RDS, respiratory distress syndrome; RR, relative risk; VLBW, very low birth weight.

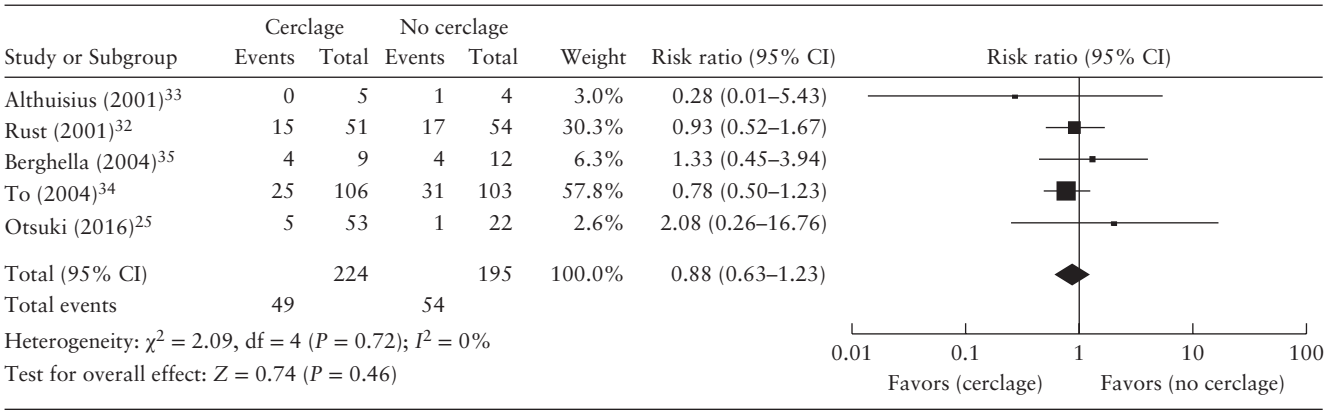

Figure 3 Forest plot for risk of preterm birth < 35 weeks in 419 women with singleton pregnancy, short sonographic mid-trimester cervical length and no prior spontaneous preterm birth (PTB), randomized to management with cerclage or no cerclage to prevent spontaneous PTB. Only first author is given for each study.

studies of high quality and with a low risk of bias according to the Cochrane risk-of-bias tools. To our knowledge, this is the largest, most comprehensive and most up-to-date meta-analysis published so far on this topic. Statistical analysis showed no significant potential publication bias, and intention-to-treat analysis was used. The statistical heterogeneity within the studies was very low. Moreover, patient-level data were used to explore for heterogeneity and maternal factors, and to perform subgroup analyses (Table 4).

The limitations of our study are inherent to the limitations of the included RCTs. The TVS-CL cut-off for intervention was different in the RCT by To *et al.*[34] compared with the rest of the included studies. Different techniques for cerclage were used among the included RCTs, but there are no definitive data to prove superiority of one technique over the other techniques and the subgroup analysis on this issue failed to reveal any significant differences. Progesterone, which is currently recommended for women with short TVS-CL[36], was not used in any of the included trials. The use of pericerclage tocolytics or antibiotics was not uniform in the included RCTs. Furthermore, most of the included RCTs routinely recommended bed rest in both the cerclage and the control groups. So far, there is no evidence supporting the use of bed rest at home or in hospital to prevent preterm delivery[37]. In a secondary analysis of an RCT of 17-α hydroxyprogesterone caproate among nulliparous

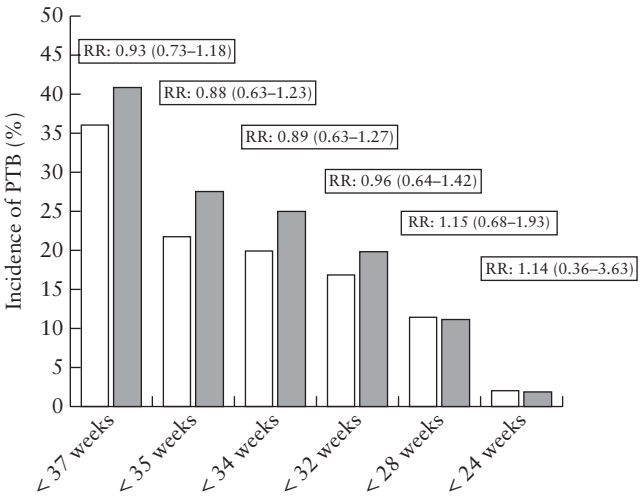

Figure 4 Incidence of spontaneous preterm birth (PTB) at < 24, < 28, < 32, < 34, < 35 and < 37 weeks in women with singleton pregnancy, short sonographic mid-trimester cervical length and no prior spontaneous PTB, randomized to management with cerclage (□) or no cerclage (■). RR, relative risk.

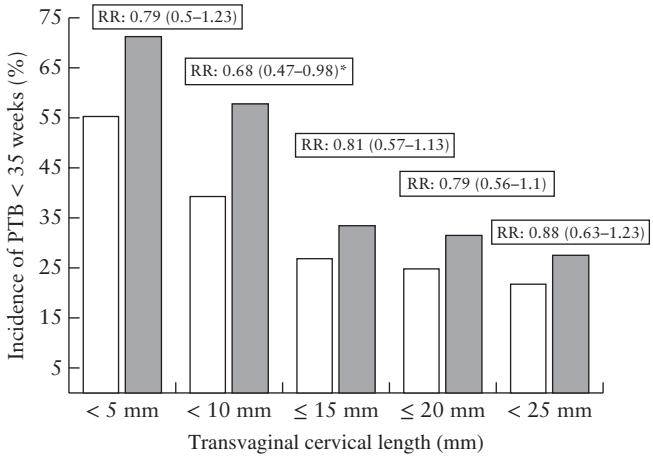

Figure 5 Incidence of spontaneous preterm birth (PTB) < 35 weeks in women with singleton pregnancy, short cervical length (CL) < 25, ≤ 20, ≤ 15, < 10 and < 5 mm on transvaginal ultrasound and no prior spontaneous PTB, randomized to management with cerclage (□) or no cerclage (■). *Statistically significant. RR, relative risk.

Table 4 Subgroup analyses for primary outcome (preterm birth (PTB) < 35 weeks) in 419 women with singleton pregnancy, short mid-trimester cervical length (CL) on transvaginal sonography (TVS) and without prior spontaneous PTB included in this systematic review and meta-analysis

Subgroup	*Cerclage*	*No cerclage*	*RR (95% CI)*	I^2 *(%)*
TVS-CL ≤ 20 mm ($n = 349$)[25,32–35]	47/188 (25.0)	51/161 (31.7)	0.79 (0.56 to 1.10)	0
TVS-CL ≤ 15 mm ($n = 305$)[25,32–35]	43/159 (27.0)	49/146 (33.6)	0.81 (0.57 to 1.13)	0
TVS-CL < 10 mm ($n = 126$)[25,32–35]	30/76 (39.5)	29/50 (58.0)	0.68 (0.47 to 0.98)*	0
TVS-CL < 5 mm ($n = 48$)[25,32–35]	15/27 (55.6)	15/21 (71.4)	0.79 (0.50 to 1.23)	0
White race ($n = 183$)[32–35]	21/95 (22.1)	33/88 (37.5)	0.59 (0.37 to 0.94)*	0
Black race ($n = 125$)[32–35]	18/57 (31.6)	20/68 (29.4)	1.07 (0.63 to 1.83)	0
Shirodkar cerclage ($n = 257$)[25,34]	29/132 (22.0)	32/125 (25.6)	0.86 (0.55 to 1.33)	0
McDonald cerclage ($n = 185$)[25,32,33,35]	20/87 (23.0)	29/98 (29.6)	0.78 (0.48 to 1.27)	0
Tocolytics and cerclage *vs* no tocolytics and no cerclage ($n = 254$)[25,32–35]	20/114 (17.5)	40/140 (28.6)	0.61 (0.38 to 0.98)*	0
Tocolytics and cerclage *vs* tocolytics and no cerclage (n = 169)[25,32,33,35]	20/114 (17.5)	18/55 (32.7)	0.54 (0.31 to 0.93)*	0
Antibiotics and cerclage *vs* no antibiotics and no cerclage ($n = 249$)[25,32–35]	20/109 (18.3)	36/140 (25.7)	0.71 (0.44 to 1.66)	0
Antibiotics and cerclage *vs* antibiotics and no cerclage ($n = 163$)[25,32,33]	20/109 (18.3)	17/54 (31.5)	0.58 (0.33 to 0.98)*	0

Values are given as *n*/*N* (%). Some data are missing as not all variables were recorded in every database. *Statistically significant. RR, relative risk.

women with singleton gestations and mid-trimester TVS-CL < 30 mm, Grobman *et al.* showed that activity restriction increased the risk of PTB < 37 weeks[38].

In one of the included trials[25], women with genital tract infection were excluded and the design of the study allowed rescue cerclage for all arms when bulging membrane was noted. The high number of subgroup analyses and secondary outcomes may lead to high risk of false-positive results. We also acknowledge that only one trial[25] was added in this meta-analysis compared with our prior review[11]. However, in this new review, IPD were used. An IPD analysis has several distinct advantages over aggregate data meta-analysis (ADMA). IPD involves the synthesis of individual-level data from the individual trials and therefore allows for the verification of published results. As IPD are available, an IPD meta-analysis allows for more flexibility regarding the inclusion and exclusion of individuals, and the choice of endpoints and subgroups, compared with ADMA. These subgroups showed potential benefit when the CL is < 10 mm and when tocolytics or antibiotics were used with cerclage. Given the low number of included trials, while no differences were found in patient characteristics available in the databases, unknown confounders cannot be ruled out.

Interpretation

Our findings provide evidence that cerclage does not prevent PTB in singleton gestations without prior spontaneous PTB but with short mid-trimester TVS CL.

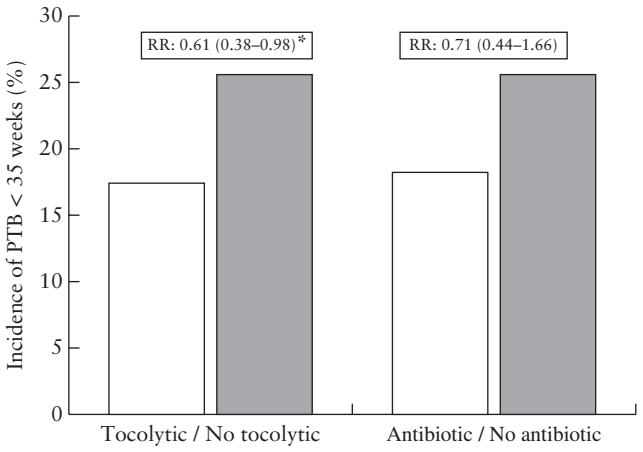

Figure 6 Incidence of spontaneous preterm birth (PTB) < 35 weeks in women with singleton pregnancy, short sonographic mid-trimester cervical length and no prior spontaneous PTB, randomized to management with cerclage (□) or no cerclage (■) and use or not of tocolytics or antibiotics as additional therapy. *Statistically significant. RR, relative risk.

Subgroup analysis of women who had TVS-CL < 10 mm, or received tocolytics or antibiotics as additional therapy to cerclage, showed that cerclage may reduce the incidence of PTB; well-powered trials should be carried out in these groups of patients. Notably, there is evidence in the literature that adjunctive perioperative tocolytics and/or antibiotics might increase the efficacy of the cervical cerclage[39]. Biological plausibility would support these results, as there are several pathways to PTB and these involve mechanical weakness of the cervix from prior surgical procedures[40] or other factors which could be treated with cerclage, infection which could be treated by antibiotics and uterine contractions which could be treated by tocolytics.

Conclusions

In summary, based on these Level-1 data, at least as used so far in these trials, there is no significant association between cervical cerclage and lower incidence of PTB in asymptomatic singleton gestations with short mid-trimester TVS-CL and without prior spontaneous PTB. Cerclage seems to be possibly efficacious at lower CLs, such as < 10 mm, and when tocolytics or antibiotics are used as additional therapy, requiring further studies in these subgroups. Indeed, with a low number of included women in our subgroup analyses, the ability to discern differences in preterm delivery is impaired by Type-II error. We observed that with 80% power and $a = 0.05$, a sample size of 103 patients in each group, for a total of 206 singleton gestations without prior spontaneous PTB but with TVS-CL < 25 mm, is required to detect a reduction in PTB < 37 weeks from a 34% baseline risk of women given vaginal progesterone[41], based on the RR of 0.54 with indomethacin, antibiotics and cerclage *vs* no tocolysis, antibiotics or cerclage; a new RCT has been initiated based on the above findings.

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Cerclaje para el cérvix corto observado mediante ecografía en gestaciones con feto único sin parto pretérmino espontáneo previo: revisión sistemática y metaanálisis de ensayos controlados aleatorizados utilizando datos individuales de pacientes

RESUMEN

Objetivo El objetivo de esta revisión sistemática y metaanálisis fue cuantificar la eficacia del cerclaje cervical en la prevención del parto pretérmino (PPT) en embarazos asintomáticos de feto único con una longitud cervical (LC) corta a mitad de trimestre observada en la ecografía transvaginal (ETV) y sin PPT espontáneo previo.

Métodos Se buscó en bases de datos electrónicas desde el inicio de cada base de datos hasta febrero de 2017. No se aplicaron restricciones de idioma. Se incluyeron todos los ensayos controlados aleatorizados (ECA) de embarazos asintomáticos con feto único y sin PPT espontáneo previo que en la ETV de mitad de trimestre presentaron una LC corta <25 mm y luego fueron asignados al azar al manejo con cerclaje o sin cerclaje. Se contactó a los autores de correspondencia de todos los ensayos incluidos para solicitar el acceso a los datos y llevar a cabo un metaanálisis de los datos individuales de las pacientes. Los datos proporcionados por los investigadores se agregaron a una base de datos maestra creada específicamente para esta revisión. El resultado primario fue el PPT < 35 semanas. Las medidas resumen se reportaron como el riesgo relativo (RR) con IC 95%. La calidad de la evidencia se evaluó utilizando el planteamiento GRADE.

Resultados Se analizaron cinco ECA, que incluían 419 gestaciones asintomáticas de feto único con ETV-LC <25 mm y sin PPT espontáneo previo. En las mujeres que fueron asignadas al azar al grupo de cerclaje, en comparación con el grupo control, no se encontraron diferencias estadísticamente significativas ni en el PPT de <35 (21,9% vs. 27,7%, RR 0,88 (IC 95% 0,63–1,23), $I^2 = 0\%$; cinco estudios; 419 participantes), <34, <32, <28 y <24 semanas, ni en la edad gestacional en el momento del parto, en la rotura prematura de membranas (PPROM, por sus siglas en inglés) o en los resultados neonatales. En las mujeres a quienes se les hizo cerclaje (en comparación con las que no se les hizo), los análisis planificados de subgrupos revelaron una tasa significativamente menor de PPT <35 semanas en mujeres con ETV-CL <10 mm (39,5% vs. 58,0%, RR 0,68 (IC 95%, 0,47–0,98), $I^2 = 0\%$; cinco estudios; 126 participantes) y en las mujeres que recibieron tocolíticos (17,5% vs. 32,7%, RR 0,54 (IC 95%: 0,31–0,93), $I^2 = 0\%$; cuatro estudios; 169 participantes) o antibióticos (18,3% vs. 31,5%, RR 0,58 (IC 95%, 0,33–0,98), $I^2 = 0\%$; tres estudios; 163 participantes) como terapia adicional al cerclaje. La calidad de la evidencia se rebajó en dos niveles debido a la alta imprecisión y por ser de tipo indirecto, y por lo tanto se juzgó como baja.

Conclusiones En gestaciones con feto único y sin PPT espontáneo previo pero con ETV-LC <25 mm en el segundo trimestre, el cerclaje no parece prevenir el parto pretérmino ni mejorar el resultado neonatal. Sin embargo, en estos embarazos, el cerclaje parece ser eficaz en LC inferiores, como las <10 mm, y cuando se usan tocolíticos o antibióticos como terapia adicional, lo que requiere estudios adicionales en estos subgrupos. Dada la baja calidad de la evidencia, hacen falta más ECA bien diseñados para confirmar los hallazgos de este estudio.

在无自发性早产既往史的单胎妊娠中超声提示宫颈缩短时行宫颈环扎术：采用个体患者水平资料进行随机对照试验的系统评价和 meta 分析

目的：本篇系统评价和 meta 分析的目的是量化在无症状单胎妊娠中宫颈环扎术预防早产（preterm birth，PTB）的效果，这些单胎妊娠孕中期经阴道超声（transvaginal sonography，TVS）提示宫颈长度（cervical length，CL）缩短且无自发性 PTB 既往史。

方法：检索电子数据库，检索时间从每个数据库建库起至 2017 年 2 月。无语种限制。纳入所有无自发性 PTB 既往史的无症状单胎妊娠的随机对照试验（randomized controlled trials，RCTs），这些单胎妊娠孕中期经 TVS 发现 CL 缩短（<25 mm），之后随机分配接受或不接受宫颈环扎术治疗。与所有纳入试验的通信作者取得联系，获取资料，并对个体患者水平资料进行 meta 分析。将研究人员提供的资料合并到为评价专门建立的主数据库中。主要结局为孕 35 周前 PTB。将综合检测结果表示为相对危险度（relative risk，RR）和 95% CI。采用 GRADE 方法评估证据质量。

结果：对 5 项 RCTs 进行分析，其中包括 419 例 TVS-CL<25 mm、无自发性 PTB 既往史的无症状单胎妊娠。随机分至宫颈环扎组的孕妇与对照组孕妇相比，孕 35 周前[21.9%和 27.7%；RR，0.88（95% CI 0.63~1.23）；I^2=0%；5 项研究，419 例研究对象]、孕 34 周前、孕 32 周前、孕 28 周前和孕 24 周前 PTB，分娩孕周，早产胎膜早破（preterm prelabor rupture of membranes，PPROM）以及新生儿结局无统计学差异。接受宫颈环扎术的孕妇与未接受宫颈环扎术的孕妇相比，预定亚组分析显示，TVS-CL<10 mm 的孕妇[39.5%和 58.0%；RR，0.68（95% CI，0.47~0.98）；I^2=0%；5 项研究；126 例研究对象]以及除宫颈环扎术外接受宫缩抑制剂[17.5%和 32.7%；RR，0.54（95% CI，0.31~0.93）；I^2=0%；4 项研究；169 例研究对象]或抗生素[18.3%和 31.5%；RR，0.58（95% CI，0.33~0.98）；I^2=0%；3 项研究；163 例研究对象]辅助治疗的孕妇孕 35 周前 PTB 发生率明显降低。由于高度不精确性和间接性，证据质量降低两级，因此为低质量证据。

结论：在无自发性 PTB 既往史但孕中期 TVS-CL<25 mm 的单胎妊娠中，宫颈环扎术似乎不能预防早产或改善新生儿结局。然而在这些孕妇中，宫颈环扎术在 CL 缩短（如<10 mm）时以及采用宫缩抑制剂或抗生素作为辅助治疗时似乎有效，需要对这些亚组进行进一步研究。由于证据质量较低，需要进行进一步精心设计的 RCTs 来证实本研究的结果。

